

Molecular mechanisms of maculopapular exanthema

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Purpose of review

Maculopapular exanthema is a common cutaneous manifestation of many diseases produced by several agents able to activate the immune system, the most common of which are drugs and viruses. In spite of its high frequency, knowledge of the molecular mechanisms involved remains scarce.

Recent findings

The cytokine patterns in maculopapular exanthema have a Th1 or Th0 pattern, according to whether the reaction is induced by a drug or a virus, respectively. Additionally, the involvement of CD4 T-lymphocytes with cytotoxic capabilities has been shown in the former. Different chemokines and their receptors are also involved in skin homing, such as CCL20, CCL27, CXCL9 or CXCL10, and oxidative stress can help exacerbate the symptoms.

Summary

These findings may be very important for the diagnostic evaluation of these entities and for the development of new tools for diagnosis and treatment.

Keywords

chemokines, cytokines, oxidative stress, skin, T-lymphocytes

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Introduction

Maculopapular exanthema (MPE) is a clinical manifestation that appears in different cutaneous and/or systemic diseases with skin involvement. It consists of diffuse cutaneous erythema with areas of skin elevation. It may evolve to vesicles or papules as part of a more severe clinical entity. Different degrees of angioedema with involvement of subcutaneous tissue may also appear. With the exception of drug allergy, few studies have been carried out over the last 10 years on the mechanisms of other identities. Drugs are the most common cause of MPE reactions [1], followed by various viruses with skin tropism, such as cytomegalovirus, parvovirus, Coxsackie's virus, paramyxovirus, toga virus and several types of herpes, such as varicella zoster, HHV6 and the gamma herpes virus of infectious mononucleosis. Exanthema can also be seen in different bacterial diseases, in patients with lymphoma [2], in graft versus host disease [3] and in diseases with other causes, such as physical agents.

The clinical manifestations of drug-induced and virus-induced exanthematic reactions have similarities, including the underlying immunological mechanisms. However, conceptual differences exist between them. From a mechanistic viewpoint, drugs are molecules that can provide a high concentration of epitopes, which can in turn activate the immunological system. They have a

known half-life in the organism and after withdrawal the drug is completely eliminated, with disappearance of the triggering mechanism. Viruses, however, enter the body and begin to interact with the molecular replicating machine, inducing a variety of clinical manifestations depending on the specific tropism. Symptoms usually have an acute onset with drug reactions and, after a period varying from hours or days up to 2 or 3 weeks after drug exposure, they then subside. If the drug administration continues after the onset of symptoms, the reaction continues, with possible worsening of symptoms in spite of symptomatic treatment. Symptoms may appear again after initial resolution and later drug re-intake, even a long time after the earlier episode. MPE is more insidious and lasts longer, however, in viral diseases. Viral skin reactions are usually accompanied by systemic involvement, whereas drug-induced exanthematic reactions are limited to the skin, unless they evolve to more severe diseases such as Stevens–Johnson–Lyell syndrome or drug hypersensitivity syndrome. Viral infections are generally followed by immunological protection, but in drug reactions re-exposure can induce the reaction again. It is therefore necessary to develop strategies to distinguish drug-induced cutaneous reactions from virus-induced reactions and within drug reactions to differentiate mild reactions from those that may evolve to more severe diseases [4]. Viruses often induce T-cell and B-cell responses, generating specific lymphocytes and antibodies [5], whereas most drugs involved in

cutaneous reactions do not induce humoral responses [6–8].

Most molecular studies over the last 5 years have concerned drug-induced exanthematic reactions. Extensive literature searches give little information about molecular studies in other types of exanthema. This review therefore concentrates mainly on drug-induced reactions, outlining the molecular mechanisms involved in drug-induced MPE (DIMPE), the most common drug-induced clinical entity.

Mechanisms of drug-induced maculopapular exanthema

Maculopapular exanthema is a common cutaneous manifestation produced after drug intake. It is important to try to reveal the molecular mechanisms involved.

Clinical findings

Virtually all drugs available for the treatment of human disease can cause DIMPE. As stated above, DIMPE consists of maculopapules of different sizes elevated over the skin, often accompanied by homogeneous redness of the skin with varying degrees of subcutaneous involvement, including edema. If the drug is stopped soon after the appearance of symptoms the lesions usually subside. Our experience has shown that exanthema does not usually evolve to more severe diseases, even in patients taking the drug for a longer time, although some scleroderma-like lesions may appear, probably induced by skin fibrosis. When the exanthema forms part of another disease, the MPE evolves to clearly distinguished vesicular lesions, the most severe of which are those appearing in the complex Stevens–Johnson–Lyell syndrome. The erythema may also represent the start of a severe response with a longer duration without the formation of papules, evolving to skin desquamation that can often be extensive. The exanthema appearing in drug reaction with eosinophilia and systemic symptom (DRESS) is accompanied by such systemic symptoms as liver involvement, and the exanthema in acute exanthematic pustulosis (AEP) has a particular skin morphology.

Pathological studies

Drug-induced MPE is considered to be induced by T-lymphocytes. This is supported by the findings of a mononuclear infiltrate predominantly surrounding blood vessels, with eosinophils in some cases. Approximately 40–70% of these cells are CD3⁺ lymphocytes, with a great number of CD4⁺ cells (Fig. 1) in the perivascular dermis [9–11]. CD4⁺ and CD8⁺ cells with hydropic degeneration of the basal layer of keratinocytes have been observed in the dermoepidermal junction [12–14]. Both cell subsets have been shown to express different mediators, such as perforin and granzyme B [15]. Some

studies have also shown interleukin (IL)-5, which contributes with other cytokines to the implication of eosinophils [16]. Regulated upon activation, normal T-cell expressed and secreted (RANTES) chemokine and the eotaxins are expressed on the affected tissue through recruitment of several cells expressing CCR3, such as eosinophils [14].

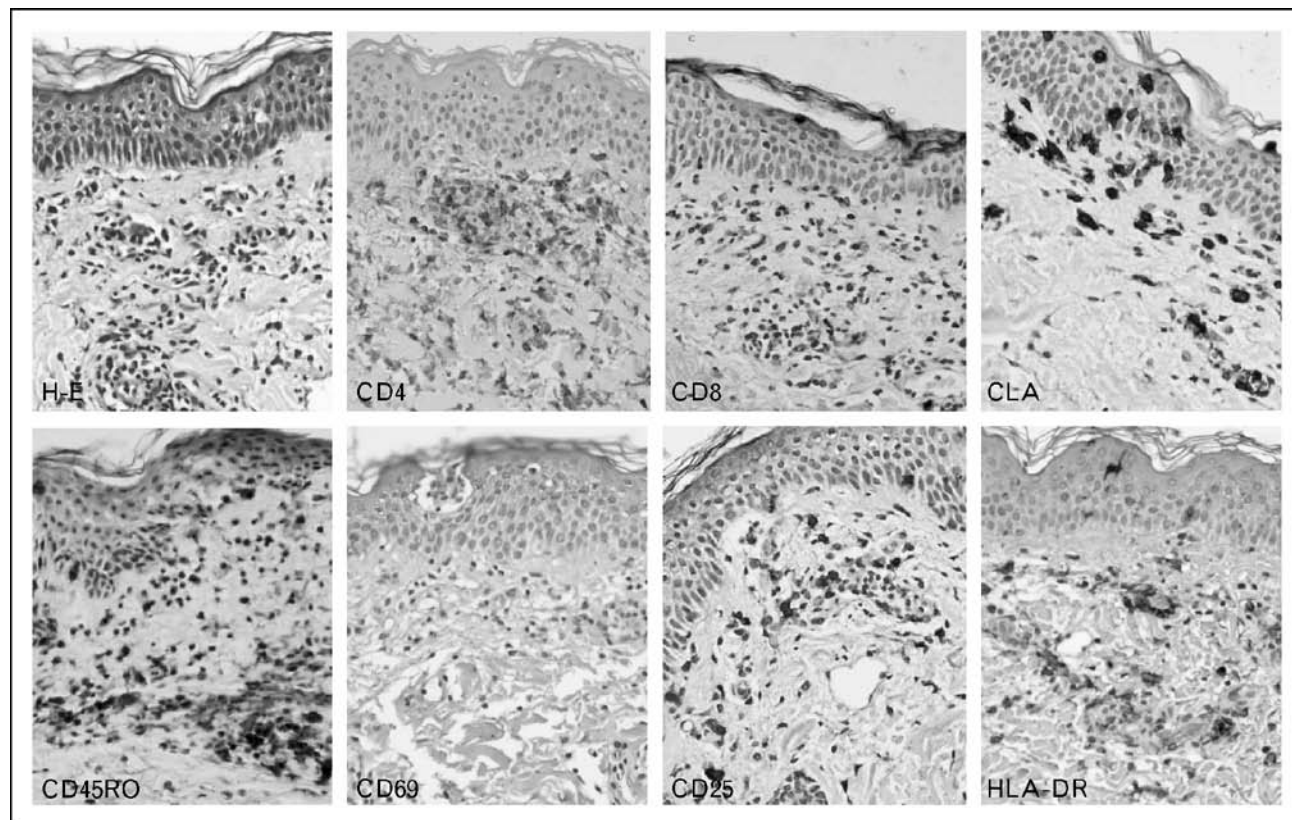
Endothelial cells and infiltrating T-cells are activated, expressing early and delayed activation markers such as CD25, the receptor for IL-2, CD69 and HLA-DR (Fig. 1). This last marker has also been found in Langerhans cells and in the basal layer of keratinocytes, conferring them with an antigen-presenting capacity [10,11,15]. These activation markers are expressed in parallel with the cutaneous homing marker cutaneous lymphocyte-associated antigen (CLA) (Fig. 1) in the acute phase of DIMPE [11], and return to normal values in the resolution phase [10]. This is in concordance with what happens in other diseases, such as atopic dermatitis or psoriasis, in which a relationship exists between the high percentage of activated T-cells expressing the CLA receptor and the evolution and severity of the reaction [17,18]. The increase in CLA and activation markers in these patients occurs in parallel in both peripheral blood and skin, proving contribution to the skin homing and recirculation of different cells involved not only in the induction of the pathological process but also in its resolution [10].

Immunological findings

Immunological studies in DIMPE have shown that drugs are recognized by lymphocytes responsible for their activation and stimulation. Detailed studies using T-cell lines and T-cell clones support the involvement of these cells in the response [19]. This has been shown with different types of drugs, such as betalactams [20], iodine contrast media [11], anticonvulsants, quinolones and antibiotics [21], heparins [22*] and others, including cytostatic agents and steroids [9]. Betalactams bind directly to different cell and serum proteins, whereas other drugs require previous metabolic conversion to become protein-reactive, such as sulfonamides and anticonvulsants. For those drugs that do not easily bind to proteins or do not generate active metabolites, such as contrast media, the involvement is more speculative although confirmed reactions exist.

Advanced studies

Improved understanding of the mechanisms involved has led to further subclassification of drug-induced T-cell reactions. From the clinical point of view DIMPE, the toxic epidermal necrolysis and Stevens–Johnson syndrome (TEN–SJS) complex, AEP, fixed drug eruption and DRESS are different entities though all are induced

Figure 1 T-cell involvement

Immunohistochemistry stain that shows the presence of CD4 and CD8 lymphocytes infiltrating the skin of MPE patients and the expression of different markers of memory (CD45RO), activation (CD69, HLA-DR) and skin homing (CLA). Results from [10].

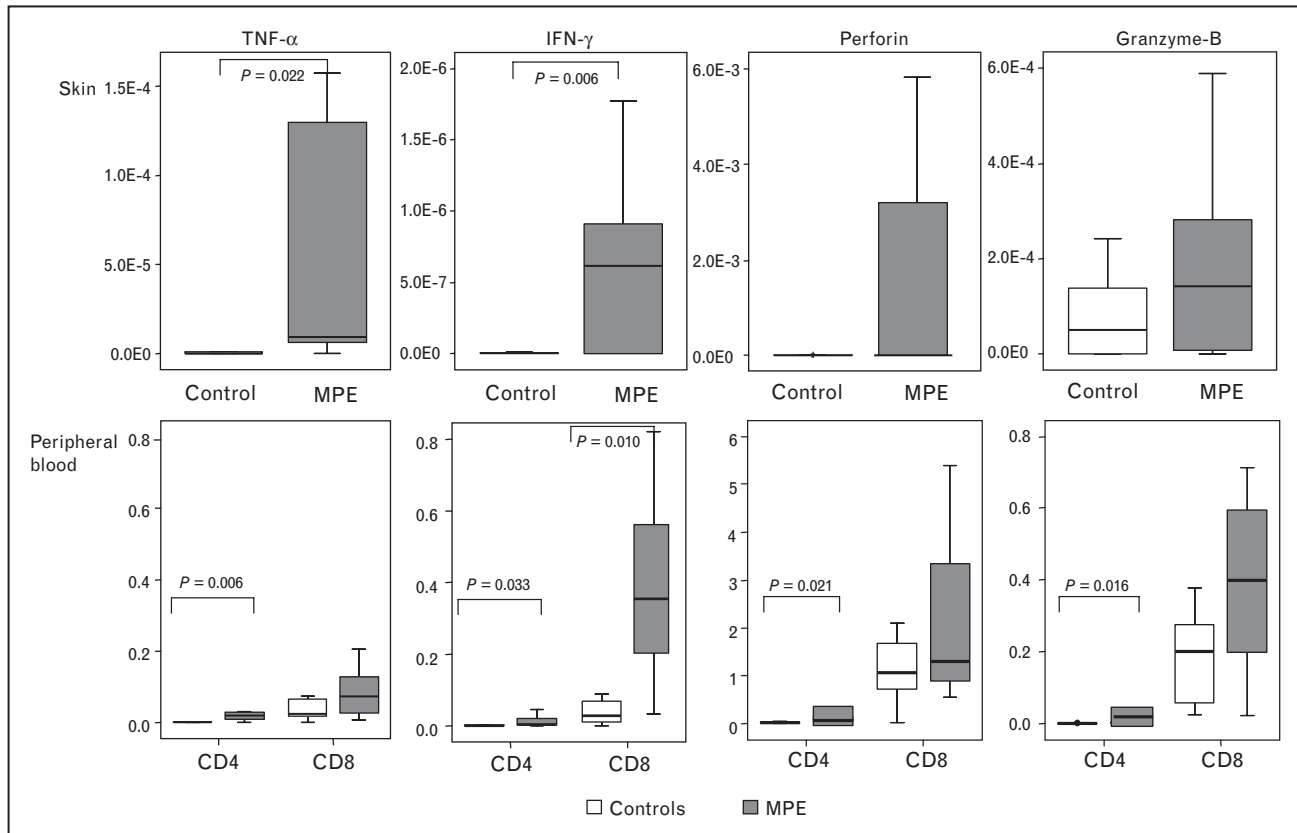
by T-cells. This has important consequences not only for the treatment and prognosis but also for the validation of the diagnostic tests, both *in vivo* and *in vitro*. Within the type IV reactions, four categories have been proposed [23], and two different pathophysiological mechanisms have been suggested for MPE: type IVb, characterized by the presence of T-lymphocytes with a Th2 pattern with IL-4 and IL-5 production and eosinophil infiltration, and type IVc, a cytotoxic response mediated by CD4⁺ and CD8⁺ lymphocytes with the production of perforin and granzyme B and with apoptosis mechanisms mediated by FAS–FASL [23]. Some studies support a well defined Th1 pattern for these reactions [9,24,25], whereas others suggest that they are not so clearly defined [16,23]. Whilst various studies show that the CD4⁺ T-cell is the main subpopulation involved in the development of DIMPE [10,15,24–28], other studies have found that the infiltrate, especially at the start, is mainly composed of CD8⁺ T-lymphocytes [12].

Monitoring the acute response by studying sequential samples from peripheral blood and skin at regular intervals not only supports an immunological mechanism but also provides valuable information for the kinetics of the

response. Different cytokine studies, including those from the chemokine family, have provided clues to understanding the mechanisms of cell recruitment. Chemokines belong to a superfamily of structurally related low-molecular-weight proteins whose functions include the regulation of leukocyte trafficking into peripheral tissues through interaction with specific receptors.

Different studies have demonstrated that Th1 cytokines and CD4⁺ T-cells have an important role in the pathogenesis of DIMPE [9,15,16,24–26]. The expression of different markers related to a Th1 phenotype, such as the cytokines interferon (IFN)- γ and tumor necrosis factor (TNF)- α (Fig. 2) and the chemokine receptor CXCR3, as well as other cutaneous homing receptors, such as CCR6 or CCR10, has been found in peripheral blood CD4⁺ cells [29^{••}]. These CD4⁺ lymphocytes have a cytotoxic role in these patients [9,15,25], because they express cytotoxic markers such as perforin, granzyme B and TNF- α (Fig. 2) [29^{••}].

A significant increase has been found in skin biopsies in the expression of chemokines and their receptors involved in a Th1 pattern (CXCL9, CXCL10 and

Figure 2 Cytokine involvement

Results from semiquantitative real-time PCR showing the higher expression of Th1 cytokines and cytotoxic markers in the skin from MPE patients and in the peripheral CD4 cells of patients with exanthema. Data from [29**]. MPE, maculopapular exanthema.

CXCR3) and in cutaneous homing (CCL20, CCL27, CCR6 and CCR10). The expression of TNF- α and IFN- γ has also been found [29**], which could be stimulating chemokine expression by the activated keratinocytes, TNF- α stimulating the expression of CCL27 [30] and IFN- γ the production of CXCL9 and CXCL10 [31]. On the contrary, several publications report TARC/CCL17 as the major chemokine responsible for lymphocyte migration to the skin in cutaneous inflammation as its specific receptor, CCR4, is expressed by the majority of CLA⁺ skin homing lymphocytes [32–35]. CCL17 shares its specific receptor, CCR4, with the chemokine CCL22, which has recently been shown to attract memory T-cells [35] and has been associated with lymphocyte recruitment to the skin in cooperation with CCL17 [36]. CCL17 and CCL22 may also cooperate in attracting CLA⁺ T-cells to the skin in DIMPE [37].

We can therefore conclude that in DIMPE, CCL17 and CCL22, through their receptor CCR4, CCL20 through CCR6 and CCL27 through CCR10, produced by cutaneous cells, are involved in the recruitment of cytotoxic CD4⁺ lymphocytes from peripheral blood to the skin,

and that CXCL9 and CXCL10, through CXCR3, recruit Th1 phenotype cells specifically.

Th1/Th2 polarization is the result of signals through cytokine receptors that culminate in the binding of specific transcription factors to multiple regulatory elements in the promoters and subsequent activation of cytokine genes. It is increasingly apparent that different transcription factors, such as T-bet, GATA-3 and c-Maf, are involved in the different types of immune responses [38]. Thus, T-bet (T-box expressed in T-cells) is related to Th1 responses, whereas the proto-oncogenes c-Maf and GATA-3 are related to Th2 commitment. T-bet plays a key role in the development of Th1 cells producing IFN- γ [39] and represses the production of Th2 cytokines, IL-4 and IL-5 [38]. In DIMPE, a Th1 pattern with T-bet has been observed in peripheral blood mononuclear cell (PBMC) and in both CD4 and CD8 T-cells [40*].

Although specific immunological mechanisms are known to be involved in DIMPE [41], concomitant nonspecific processes such as oxidative stress can also play a role, by

amplifying the specific response or influencing its severity and duration [42]. Oxidative stress involves an imbalance in the levels of reactive oxygen species, which are not adequately scavenged by antioxidant enzymes such as Cu/Zn-superoxide dismutase (SOD), catalase (CAT) or cellular glutathione peroxidase (GPX) [42]. The antioxidant enzymes have been shown to modulate the expression of a variety of inflammatory molecules in several immunological diseases, such as atopic dermatitis, psoriasis and asthma [43,44]. Data show that SOD activity is significantly increased in DIMPE. When carbonylation of proteins (a marker of protein damage) was used as an index of the oxidative damage, there was a significant increase in DIMPE compared with control groups [45].

Virus-induced exanthematic reactions

Viruses are the second most important cause of MPE in children, although they are less frequent in adults. Mechanisms of the adaptative immune response against viruses are mediated by T-lymphocytes, although in some instances both T-cell and B-cell responses with the production of cytotoxic T-cells and antibodies of different isotypes can occur. Viruses with skin tropism include the herpes group, such as varicella zoster, responsible for chicken pox; the Epstein–Barr virus, a gamma herpes virus inducing infectious mononucleosis and HHV6, which produces a MPE also known as xanthema subitum, or the cytomegalovirus. Exanthematic reactions include measles, produced by a paramyxovirus-like virus' rubella, induced by togavirus, and the erythema infections of the Fifth disease, induced by parvovirus B19.

A study comparing the immunologic mechanisms involved in DIMPE versus those induced by viruses (VIMPE) has shown a high percentage of activated skin-homing CLA⁺ memory T-cells in the former, paralleling the clinical course of the disease and returning to baseline values within 45 days. In cases of VIMPE, there were only a moderate percentage of activated T-cells, significantly higher when compared to controls and with a nonsignificant increase in the percentage of CLA⁺ memory T-cells, in clear contrast with DIMPE. Analysis of the cytokine expression in PBMC in the acute phase of the reaction showed a Th1 pattern in DIMPE, with production of IL-2, IFN- γ and TNF- α , but a Th0 pattern in VIMPE, with production of IL-4, IL-10, IFN- γ and TNF- α [46]. Further studies are required to differentiate the patterns in these responses.

Virus and drug interactions

Viral infections can interact at different points during an adverse drug response, including drug metabolism and lymphocyte presentation or the effector response induced by T-cells. The most common clinical manifesta-

tion in which viruses can act as cofactors is ampicillin-induced exanthema in infectious mononucleosis [47^{••}]. Over the last few years an increase in drug reactions has been reported in HIV patients [47^{••}] and the reactivation of HHV-6 after allergic reactions to drugs [48].

Infectious mononucleosis is an acute disease caused by the Epstein–Barr virus and characterized by atypical B-cell and T-cell expansion of activated lymphocytes in peripheral blood. More than 70% of these are CD8⁺ T-cells and up to 44% specifically recognize the Epstein–Barr virus [47^{••}]. The intake of ampicillin increases the percentage of exanthema from 28.8 to 69% in adults and up to 100% in children. Ampicillin is well tolerated in these patients after resolution of the viral infection, although a few patients have allergic reactions and positive skin tests a long time after resolution [49,50].

Patients with HIV suffer a high incidence of acute drug-induced cutaneous reactions. Evidence exists in these patients of an early reactivation of the Epstein–Barr virus during an immune response to drugs [47^{••}].

Drug reactions with eosinophilia and systemic symptoms are mainly produced by anticonvulsants, sulfonamides and allopurinol, amongst other drugs. As occurs with viral reactions, the MPE can progress to exfoliative dermatitis, lymphadenopathy, hepatitis and hematological abnormalities such as leukocytosis, eosinophilia and an atypical lymphocytosis with a high percentage of CD8 cells. In many cases resolution is slow, with recurrence of symptoms associated with reactivation of an HHV6 infection. One possibility for this reactivation is that these drugs can induce a temporary hypogammaglobulinemia favoring viral reactivation [51]. Anticonvulsants have also been suggested to induce an immunosuppressive state that favors viral reactivation [48].

Diagnostic approach

Exanthematic reactions can be evaluated in two different ways, either at the moment of occurrence or after resolution. Evaluation of the reaction during the occurrence enables detailed clinical observation that helps to identify viral or drug agents or other possible causes. At this stage detailed virologic studies, such as antibody measurement, and more sophisticated approaches, such as PCR studies, may enable a viral cause to be identified or ruled out. At present, the only utility of immunological studies in acute drug reactions is to monitor the response and obtain information for research on the mechanisms involved. Most patients with DIMPE are evaluated from months to years after the episode. In these circumstances, virologic studies are of little value and few diagnostic tests are available to show the drug involved in the DIMPE.

The value of skin testing has mostly been shown in single case reports, with only a few case series enabling evaluation of sensitivity and specificity. Intradermal and patch testing has been used with different drugs. Apart from penicillins, the other series involve just a few cases and usually many drugs are involved. Detailed studies and guidelines for application and interpretation have been published. These tests have a good specificity when used at the recommended concentrations, but sensitivity is not optimal. Although a sensitivity greater than 50% has been reported for betalactam-related cases [52], recent studies in well validated series indicate that this is not the case and it may in fact be lower than 20% [53^{••}]. Sensitivity may improve in more severe reactions but this has yet to be studied.

In-vitro assays have been carried out for the diagnosis of DIMPE. Most of these studies were undertaken in various types of nonimmediate drug reactions and with different drugs. Studies with DIMPE alone and just one type of drug are scanty. A study using amoxicillin and ampicillin showed a reasonable sensitivity and specificity but further studies are required. A recently described method using simultaneously lymphocytes and dendritic cells in patients with DIMPE to amoxicillin has shown promising results, although further evaluation is required [20].

Conclusion

Because exanthema is the most common manifestation of drug-induced reactions and in many instances it is also an expression of viral diseases, an appropriate diagnostic workup should be done. However, this is not always possible. Drug-induced reactions pose a major problem, especially when they are evaluated retrospectively.

In a certain proportion of patients specific peripheral T-lymphocytes are stimulated by the drug and, as stated above, this can be used in diagnostic testing. However, more detailed studies are needed and in-vitro assays should be improved in order to be useful and realistic. Monitoring the acute response is a rational strategy that may enable discrimination between viral-induced and drug-induced reactions and even anticipate the clinical course and the prognosis. However, further research is required to establish precisely which markers are useful for this purpose.

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